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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/319,092	06/18/1999	MICHAEL TEWES	TEWESETAL	2371

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EXAMINER

LEE, SHUN K

ART UNIT	PAPER NUMBER
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2884

DATE MAILED: 08/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/319,092

Applicant(s)

TEWES ET AL.

Examiner

Shun Lee

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 2/8/06, 3/13/06 & 6/8/06.
2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 22-25, 28, 31, 32, 35-40 and 42-49 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 22-25, 28, 31, 32, 35-40 and 42-49 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☒ The drawing(s) filed on 06 December 2002 and 15 August 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 20060208.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 22-24 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobsen (US 5,329,352) in view of Engelhart *et al.* (WO 96/06377 with corresponding US 5,903,688), Qian *et al.* (Applied Optics 30:1185-1195, April 1991), and Schalz (US 5,585,964).

In regard to claims **22-24** and **36**, Jacobsen discloses (Figs. 1-3) an apparatus comprising:

(a) a support body (21, 31);

- (b) a pinhole array (8) comprising at least one pinhole (8) coupled to said support body (21, 31);
- (c) at least one fluorescence detector (11) coupled to said support body (21, 31);
- (d) a lens array (10) comprising at least one lens (10), coupled to said support body (21, 31), and positioned between at least one pinhole (8) in said pinhole array (8) and said at least one detector (11), said lens array (10) for focusing an emission light passing through said at least one pinhole (8) and onto said at least one detector (11); and
- (e) a plurality of dichroic beam splitters comprising a first dichroic beam splitter (7) and at least a second dichroic beam splitter (9) coupled to said support body (21, 31) in a beam path and wherein at least one pinhole (8) from said pinhole array (8) is disposed between said first dichroic beam splitter (7) and said at least a second dichroic beam splitter (9) wherein a beam is focused between said first (7) and said at least a second (9) dichroic beam splitters and wherein said beam is a fluorescence beam (column 1, lines 31-40) and is detected by said at least one fluorescence detector (11) to determine a fluorescence of a specimen (5) disposed outside the support body (21, 31).

While Jacobsen also discloses (column 1, lines 31-40; column 4, lines 32-47) that the apparatus comprises a commercial confocal laser scanning microscope (CLSM) wherein the stimulating light for exciting fluorescence emission is supplied by a laser (1), the apparatus of Jacobsen lacks an explicit description of a fiber optic waveguide disposed within the coupling connection coupled to the support body for coupling in a

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stimulating light and that the support is made in one piece from a metallic material having a connection flange for attachment to an optical inlet and outlet of a microscope as a fluorescence correlation spectroscopy module outside the body of the microscope. However, commercially available confocal laser scanning microscopes are well known in the art. For example, Engelhart *et al.* teach (column 1, lines 34-42; Fig.) to couple a laser (1) to a microscope via an optical module (8) having an optical fiber (4) to isolate the laser (1) from the microscope and Schalz teaches (column 4, lines 1-25) that modularly designed microscopes should be manufactured of metal such as aluminum or brass in a one-piece construction-type in order to increase rigidity. Schalz also teaches (column 6, lines 29-40) that a modular microscope system makes it possible to attach modules (*i.e.*, support body) via precision attachment surfaces (*e.g.*, connection flange) without additional alignment or optical adjustment. Further, Qian *et al.* teach (second paragraph on pg. 1186) it is known in the art that "Most FCS and FPR experiments are carried out on a standard epifluorescence microscope which is coupled to a laser in a confocal geometry". Therefore it would have been obvious to one having ordinary skill in the art at the time of the invention to manufacture the modules in the apparatus of Jacobsen as a metallic one-piece construction-type that can be attached to a precision attachment surface of a modular microscope, in order to have rigid module with a fiber optic waveguide coupling connection that can be attached to a microscope without additional alignment or optical adjustment while isolating elements (such as the laser which provides the stimulating light) from the microscope so as to obtain fluorescence

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data in well known fluorescence experiments such as FCS (*i.e.*, fluorescence correlation spectroscopy).

4. Claims 25 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobsen (US 5,329,352) in view of Engelhart *et al.* (WO 96/06377 with corresponding US 5,903,688), Qian *et al.* (Applied Optics 30:1185-1195, April 1991), and Schalz (US 5,585,964) as applied to claim 22 above, and further in view of Chande (US 4,844,574).

In regard to claim **25** which is dependent on claim 22, the modified apparatus of Jacobsen lacks a collimator for generating a parallel light beam that is disposed within said support body in an excitation beam path after said coupling connection. Chande teaches (column 3, lines 19-25; Fig. 1) to provide a collimator (108) in order to intercept the fiber emitted beam (column 3, lines 19-25). Therefore it would have been obvious to one having ordinary skill in the art at the time of the invention to provide a collimator in the modified apparatus of Jacobsen, in order to intercept and collect the fiber emitted beam as taught by Chande.

In regard to claim **39** which is dependent on claim 22, the modified apparatus of Jacobsen lacks a collimator is tuned to the numerical aperture of the fiber optical waveguide. Chande teaches that the focal length (f_1) and clear aperture (*i.e.*, parallel light beam diameter D_1) of the collimator (108) must be selected in order to intercept the fiber emitted beam (column 3, lines 19-25). It is noted that the numerical aperture is defined as the sine of half the acceptance angle (*i.e.*, see θ_{EM} in Fig. 1 of Chande). Therefore it would have been obvious to one having ordinary skill in the art at the time

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of the invention to match the focal length and clear aperture (*i.e.*, numerical aperture) of the collimator to the emitted beam angle (*i.e.*, numerical aperture) of the fiber in the modified apparatus of Jacobsen, in order to intercept and collect the fiber emitted beam as taught by Chande.

5. Claims 28, 31, 32, 35, 37, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobsen (US 5,329,352) in view of Engelhart *et al.* (WO 96/06377 with corresponding US 5,903,688), Qian *et al.* (Applied Optics 30:1185-1195, April 1991), and Schalz (US 5,585,964) as applied to claim 22 above, and further in view of Jörgens (US 5,535,052).

In regard to claim **28** which is dependent on claim 22, the modified apparatus of Jacobsen lacks a filter array (*e.g.*, at least two frequency selective filter devices) and the beam splitter are set on a receptacle holder removably inserted within the support body. Schalz teaches that holding elements (*i.e.*, sliders, carriers, or slide-in-modules; see column 2, lines 36-54) have " ... corresponding precision-stop-surfaces ... for the exact positioning of the holding element ... " (see also column 4, lines 21-23) and that these holding elements are designed to contain optical elements such as fluorescence-dividing cubes with switching positions (column 2, lines 60-67). Jörgens teaches (column 5, lines 47-53) that filter, beam splitters, and/or mirrors are used to provide a plurality of confocal detection channels. Therefore it would have been obvious to one having ordinary skill in the art at the time of the invention to provide beam splitters with associated filters in a removably inserted common receptacle holder (*i.e.*, sliding mechanism) in the modified apparatus of Jacobsen, in order to select particular

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combinations of beam splitter with associated filters so as to obtain a desired range of wavelengths in each of a plurality of confocal detection channels.

In regard to claims **31** and **32** which are dependent on claim 28, the modified apparatus of Jacobsen lacks at least one mirror. Jörgens teaches (column 5, lines 47-53) that filter, beam splitters, and/or mirrors are used to provide a plurality of confocal detection channels. Therefore it would have been obvious to one having ordinary skill in the art at the time of the invention to provide at least one mirror in the modified apparatus of Jacobsen, in order to obtain a plurality of confocal detection channels.

In regard to claim **35** which is dependent on claim 28, the modified apparatus of Jacobsen lacks a detailed description of the receptacle holder (*i.e.*, slider), characterized in that the support body (4) for receiving the receptacle holder (15) is provided with shaped surfaces (25), to which the receptacle holder (15) provided with complementarily shaped surfaces arrayed on the support body in the beam path can be fixed. Schalz teaches that holding elements (*i.e.*, sliders, carriers, or slide-in-modules; see column 2, lines 36-54) have " ... corresponding precision-stop-surfaces ... for the exact positioning of the holding element ... " (see also column 4, lines 21-23) and that these holding elements are designed to contain optical elements such as fluorescence-dividing cubes with switching positions (column 2, lines 60-67). Therefore it would have been obvious to one having ordinary skill in the art at the time of the invention to provide corresponding precision-stop-surfaces in the sliders of the modified apparatus of Jacobsen, in order to have exact positioning and alignment of the optical elements in the sliders as taught by Schalz.

In regard to claim **37** which is dependent on claim 28, the modified apparatus of Jacobsen lacks that the support body is made with cavities for receiving the receptacle holder, wherein the said cavities have suitable lateral surfaces designed to accommodate the oriented reception of the receptacle holder. Schalz teaches that a carrier (*i.e.*, receptacle holder) has corresponding precision-stop-surfaces (*e.g.*, lateral surfaces of a cavity) for exact positioning (column 2, lines 46-59) without additional alignment or optical adjustment (column 6, lines 29-40). Therefore it would have been obvious to one having ordinary skill in the art at the time of the invention to provide cavities with corresponding precision-stop-surfaces in the modified apparatus of Jacobsen, in order to have exact positioning without additional alignment or optical adjustment as taught by Schalz.

In regard to claim **38** which is dependent on claim 37, Schalz and Jörgens is applied as in claims 28, 31, 32, and 35 above.

6. Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobsen (US 5,329,352) in view of Engelhart *et al.* (WO 96/06377 with corresponding US 5,903,688), Qian *et al.* (Applied Optics 30:1185-1195, April 1991), Schalz (US 5,585,964), and Chande (US 4,844,574) as applied to claim 39 above, and further in view of Jörgens (US 5,535,052).

In regard to claim **40** which is dependent on claim 39, Schalz and Jörgens is applied as in claims 28, 31, 32, 35, 37, and 38 above.

7. Claims 42-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobsen (US 5,329,352) in view of Engelhart *et al.* (WO 96/06377 with corresponding

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US 5,903,688), Qian *et al.* (Applied Optics 30:1185-1195, April 1991), Schalz (US 5,585,964), and Jörgens (US 5,535,052).

In regard to claim **42**, Jacobsen in view of Engelhart *et al.* and Qian *et al.* is applied as in claims 22-24 above. Schalz and Jörgens is applied as in claims 28, 31, 32, 35, 37, and 38 above. Jacobsen also discloses (Figs. 1-3) that the beams passes through or reflect from the plurality of beamsplitters (7, 9).

In regard to claim **43**, Jacobsen in view of Schalz, Engelhart *et al.*, Qian *et al.*, and Jörgens is applied as in claim 42 above. The apparatus of Jacobsen lacks that each of the optical components and said at least one mirror can be removed from the support body and inserted in a different order in a different one of said plurality of cavities or rotated 180° and reinserted. Schalz teaches (column 5, lines 8-20) a fluorescence-divider turret (31 in Figs 1a and 1b) inserted as a slide in module. Therefore it would have been obvious to one having ordinary skill in the art at the time of the invention to provide a fluorescence-divider turret in the apparatus of Jacobsen, in order to select a particular combination of beam splitter with associated filters (*i.e.*, a particular fluorescence-divider) by sliding in the (*e.g.*, 180°) rotated fluorescence-divider turret module so as to obtain a desired range of wavelengths in the confocal detection channel.

In regard to claim **46**, Jacobsen in view of Schalz, Engelhart *et al.*, Qian *et al.*, and Jörgens is applied as in claim 42 above. Jacobsen also discloses (Figs. 1-3) that the focal point of said emission light is after said beam splitter (7) and a focal point of said stimulation light is before said beam splitter (7).

In regard to claim **47**, Jacobsen in view of Schalz, Engelhart *et al.*, Qian *et al.*, and Jörgens is applied as in claim 42 above. Jacobsen also discloses (Figs. 1-3) that a focal point of said stimulation light is before said beam splitter (7).

In regard to claims **44**, **45**, **48**, and **49**, Jacobsen in view of Schalz, Engelhart *et al.*, Qian *et al.*, and Jörgens is applied as in claims 46 and 47 above.

Response to Arguments

8. Applicant's arguments filed 8 February 2006 have been fully considered but they are not persuasive.

Applicant argues (last paragraph on pg. 16 to first paragraph on pg. 18 of remarks filed 8 February 2006) that there is no suggestion to combine the references of Jacobsen, Engelhart *et al.*, and Qian *et al.* since these microscopes are all designed entirely different from each other and no person skilled in the art would replace the photoelectric detector (11) in Jacobsen, with a time depending detector as required for fluorescence correlation spectroscopy. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it is important to recognize that fluorescence correlation spectroscopy comprises data analysis of time resolved fluorescence spectroscopy data

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(see e.g., Qian *et al.*). It should also be noted that the microscope of Engelhart *et al.* is a confocal laser scanning microscope (abstract) and the microscope of Qian *et al.* is a modified confocal laser scanning microscope ("Although the system just described and the standard scanning confocal fluorescence microscope are similar overall,^{11,12} they differ in certain respects. Scanning is not required in conventional FCS or FPR, although it can be useful in specific situations.¹³⁻¹⁵"; last paragraph in left column on pg. 1187). In addition, Jacobsen states (column 2, line 47 to column 3, line 17) that "As a confocal scanning light microscope, all arrangements are suitable in which the sample piece is scanned by a focusing light beam and in which a portion of the transmitted or scattered light is imaged by an imaging optical beam path onto an aperture or onto a system of apertures and in which the portion of said light passing through the aperture is measured by a photoelectric detector and, with the aid of said measuring signal, an image of the entire sample piece is produced. ... The spectroscopic measuring processes may be any methods which are based on recording the wavelength-dependent intensity of visible light or of light having a wavelength in the vicinity of visible light, e.g. of 100 nm to 20 μm . Methods to be cited in particular are absorption spectroscopy in the ultraviolet, visible, near-infrared and infrared region as well as fluorescence and Raman spectroscopy. ... As a simultaneously recording spectrometer, all arrangements may be cited which allow, for the entire wavelength range applicable to the spectroscopic process in question or for parts thereof, time resolution measurement of the radiant intensity contained in the measuring light per wavelength interval" and (column 4, lines 42-47) that "A commercial CLSM 21 is combined with a

commercial triple spectrograph 16 in that a portion of the measuring light passing through the measuring aperture is separated from the measuring channel of the CLSM by a beam splitter 9 and introduced by way of the optical fibres 24 into the spectrograph". Thus the microscope of Jacobsen is a confocal laser scanning microscope and Jacobsen expressly teach time resolved fluorescence spectroscopy measurements with confocal geometry provided by the confocal laser scanning microscope.

Applicant argues (last paragraph on pg. 18 of remarks filed 8 February 2006) that the proposed modification would change the principle of operation of Jacobsen since the proposed modification would no longer be a process for producing and correlating light microscope images and spectroscopic data as state in column 1, lines 6-8 of Jacobsen. Examiner respectfully disagrees. As discussed above, Jacobsen expressly teach time resolved fluorescence spectroscopy measurements with confocal geometry provided by a confocal laser scanning microscope. Therefore, the proposed modification would not change the principle of operation of Jacobsen since Jacobsen is also directed to time resolved fluorescence spectroscopy measurements with the confocal geometry provided by a confocal laser scanning microscope.

Applicant argues (last paragraph on pg. 19 to second paragraph on pg. 20 of remarks filed 8 February 2006) that the Jacobsen microscope cannot be a fluorescence correlation spectroscopy microscope since it is specialized for correlating light microscope images and spectroscopic data not a standard epifluorescence microscope images with an optical path between the dichroic beam splitter and the detector that is

much too long and unstable. These arguments are not persuasive since applicant fails to provide any evidence that the confocal laser scanning microscope of Jacobsen is unstable and cannot perform time resolved fluorescence spectroscopy measurements such as fluorescence correlation spectroscopy.

Applicant argues (last paragraph on pg. 20 of remarks filed 8 February 2006) that Qian *et al.* would require undue experimentation since Qian *et al.* only suggest to couple the microscope to a laser in confocal geometry but does not teach in detail how a standard microscope is to be changed for FCS measurements. Examiner respectfully disagrees. Qian *et al.* provides detail descriptions of FCS measurements in confocal geometry (see *e.g.*, Fig. 1).

Applicant argues (two paragraphs on pg. 21 of remarks filed 8 February 2006) that the combination of cited prior art does not teach or suggest a support body disposed outside of the main body microscope. Examiner respectfully disagrees. Schalz teaches (column 6, lines 29-40) that a modular microscope system makes it possible to attach modules (*i.e.*, support body) via precision attachment surfaces (*e.g.*, connection flange) without additional alignment or optical adjustment. Therefore, the cited prior art suggest that a modular microscope system (*e.g.*, a support body disposed outside of the main body microscope) achieves the desirable attribute of rapid attachment and detachment of modules.

Applicant argues (second paragraph on pg. 22 of remarks filed 8 February 2006) that the claims are allowable since there is no direct suggestion to combine the cited references and the claims have been allowed in Europe. First it is noted that claims

which have been allowed in Europe does not imply that that the claims satisfy the conditions for patentability as required by 35 U.S.C. and 37 CFR. Further as discussed above, examiner respectfully disagrees that there is no suggestion to combine the cited references.

Conclusion

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shun Lee whose telephone number is (571) 272-2439. The examiner can normally be reached on Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Porta can be reached on (571) 272-2444. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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